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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/241,347	02/02/1999	HERMANN BUJARD	BBI-009C4CN	8608

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/241,347	BUJARD ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,4,5,7-10,13,15 and 26-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-10,13,15 and 26-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Application is a CON of 08/486,814, filed June 7, 1995, now U.S. Patent No. 5,866,755, which is a CIP of 08/383,754 filed February 3, 1995, now U.S. Patent No. 5,789,156, which is a CIP of 08/275,876, filed July 15, 1994, now U.S. Patent No. 5,654,168, which is a CIP of 08/270,637 Filed July 1, 1994, now abandoned and is a CIP of 08/260,452, filed June 14, 1994, now U.S. Patent 5,650,298, which is a CIP of 08/076,327 filed June 14, 1993, now abandoned, and is a CIP of 08/076,726, filed June 14, 1993, now U.S. Patent No. 5,464,758.

According to the Amendment filed by the Applicant October 20, 2004, claims 1, 2, 4, 5, 7-11, 13, 16, 18, 19, 21-28 were pending in the application. Claims 1, 2, 4, 8, 10, 13, 15, 26, 27, 28 have been amended. New claims 29-46 have been added. Claims 3, 11, 14, 16, 18, 19, 21-25 have been cancelled.

Claims 1, 2, 4, 5, 7-10, 13, 15, 26-46 are pending.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 20, 2004 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7-10, 13, 15, 26-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse having a transgene integrated into the genome of the mouse and also having a tet operator-linked gene of interest in the genome of the mouse, wherein: the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which is a Tet repressor or mutated Tet repressor that binds to a tet operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein the transgene is expressed in cells of the animal at a level sufficient to produce amounts of the fusion protein that are sufficient to inhibit transcription of the tet operator-linked gene of interest, wherein said gene of interest confers a detectable and functional phenotype on the mouse when expressed in the cells of the mouse, wherein the level of transcription of the tet operator-linked gene is increased or decreased in the absence or presence of tetracycline or a tetracycline analogue, does not reasonably provide enablement for any other embodiments for reasons of record set forth in the previous actions of 7/8/99, 9/13/01, 5/21/03, and 4/20/04. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The Applicants' arguments filed 8/20/04 have been fully considered, but they are not persuasive. The Examiner maintains that the claims, written broadly, are to any animal made with the tet system described by the Applicants, including the animals with no utility.

The Applicants state that the pending claims do not recite a phenotype limitation (page 10, paragraph 2, in bold and italics). The Applicants state that the claimed invention is directed to a transgenic non-human animal comprising a tet-based gene expression regulatory system, wherein transcription of a tet-operator linked gene of interest depends on the presence or absence of tetracycline or an analogue thereof. Transcription of the tet-operator linked gene is dependent upon the bound state of the inhibitor fusion protein on the tet operator. Thus, the "phenotype" resulting from the tet gene regulatory system is one of active or inactive gene expression.

While the Applicant argues that the pending claims do not recite a phenotype limitation, the Examiner disagrees. The claims are to the animal and with it, all the properties inherent to the animal. In particular, if the Applicants are claiming an animal system encompassing the ability to increase or decrease transcription of the tet-operator-linked gene (e.g. claim 1, fourth indentation, lines 2-3), then the Applicants must account for this aspect of the invention. As a result of changing expression of the tet-operator-linked gene, phenotypes in the animal are generated. Regardless whether the Applicants intended to claim the phenotypes, they are inherent to the transgenic animal and must be accounted for.

With regards to the situation of directing the definition of "phenotype" to the change of gene expression of the gene under tet operator control, is that regardless of changing the expression level of the gene under the control of the tet operator, the end result remains as to whether or not the skilled artisan is enabled to use the animal at hand. Although the Applicants stress that the "phenotype" is the change in gene

expression of the gene under tet operator control, nothing in the specification teaches a skilled artisan what to do with an animal that has changes in gene expression but has no subsequent biological mechanism, i.e., phenotype, to study. The fact that not every gene that is targeted by this tet system will result in an animal with a phenotype, is the issue needs to be addressed, in order for any animal to be encompassed by the claims. It should be pointed out that if an animal with changes in gene expression, but has no discernable phenotype is claimed by an Applicant, that animal would raise issues of specific and substantial utility under 35 U.S.C. § 101. It then follows that a skilled artisan would then not be enabled to use an animal without a phenotype because no comparative studies could be carried out between a wild type animal and the mutant. Although the Applicant has amended the claims to emphasize the "phenotype" of altered level of operator-linked gene expression in any animal, the claims still encompass animals made with the tet system that have no discernable biological mechanism to study. For this reason, the claims are not enabled.

The enablement issue that was prompted in previous Office Actions is related to the claims broadly encompassing animals made with the tet system and having no phenotype in the following way. This issue concerns the fact that while the art has demonstrated much functional and structural homology between proteins, there are instances where proteins homologous between different species of animals will have different biological functions. In the case discussed in previous Office Actions, Hammer et al. (1990, Cell 63:1099-1112) demonstrated that transgenic mice that overexpressed human HLA-B27 and human β2-microglobulin (hβ2m) were not a good model for a

human disease, whereas a rat that overexpressed human HLA-B27 and human β2-microglobulin (hβ2m) was. The bottom line inferred from Hammer et al. is that one cannot assume all biological processes are the same between animals. One way of accounting for this difference is at the molecular level, such as via promoters and enhancers. If there are differences between promoters and enhancers between animals, this must also suggest that there are differences in transcription factors that interact with these regulatory regions. Thus, it would follow that some genes are regulated differently between species. Because of this difference, one cannot generate a transgenic animal and expect that expressing the same gene in other species of animals will be the same. With regards to the instant Application, one cannot expect that changes of gene expression (i.e. the gene under control of the tet operator) using the tet system in two species of animals will necessarily have the same biological effect. While the Examiner is not as concerned with the issue that arises when two species of animals result in two different phenotypes when the homologous proteins are targeted, the Examiner is more concerned with the issue when one animal has a phenotype and the second animal has no phenotype. Again, as described above, the animal with no phenotype starts to raise issues of utility and enablement. For this reason, one cannot make the assumption that because one transgenic was made, the invention is enabled for all other species of animals.

In view of the quantity of experimentation necessary, lack working examples, nature of the invention, state of the prior art, the unpredictability of the art, and breadth

of the claims, at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claims 1, 2, 4, 5, 7-10, 13, 15, 26-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While the arguments provided by the Applicants have been considered, they have not been found persuasive.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at: http://www.uspto.gov/web/menu/current.html#register).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification is adequate in teaching a transgenic mouse having a transgene integrated into the genome of the mouse and also having a tet operator-linked gene of interest in the genome of the mouse, wherein: the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which is a Tet repressor or mutated Tet repressor that binds to a tet operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein the transgene is expressed in cells of the animal at a level sufficient to produce amounts of the fusion protein that are sufficient to inhibit transcription of the tet operator-linked gene of interest, wherein said gene of interest confers a detectable and functional phenotype on the mouse when expressed in the cells of the mouse, wherein the level of transcription of the tet operator-linked gene is increased or decreased in the absence or presence of tetracycline or a tetracycline analogue, the specification fails to adequately describe other species of animals having the same embodiments of the mouse described. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant

identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, Applicants have disclosed a transgenic mouse comprising a tet system described by the Applicants. However, while the specification teaches examples of a mouse wherein the tetO-linked gene is luciferase (e.g. page 62, "Generation of mice for the $P_{hCMV^{*}-1}$-luciferase reporter unit"), the specification does not generally teach a skilled artisan mice wherein the tetO-linked gene is any gene. The ramification of this is that the specification must then account for every gene under the tetO control and the subsequent phenotype that ensues when the gene under tetO control is expressed (or repressed). The primary issue is that not all genes will result in a phenotype and not all genes will predictably result in a phenotype, even though another species of animals has a phenotype for that gene. The skilled artisan cannot envision what genes will result in phenotypes in which animals and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a transgenic mouse having a transgene integrated into the genome of the mouse and also having a tet operator-linked gene of interest in the genome of the mouse, wherein: the transgene comprises a transcriptional regulatory element functional in cells of the animal operatively linked to a polynucleotide sequence encoding a fusion protein which inhibits transcription in eukaryotic cells, the fusion protein comprising a first polypeptide which is a Tet repressor or mutated Tet repressor that binds to a tet operator sequence, operatively linked to a heterologous second polypeptide which inhibits transcription in eukaryotic cells, wherein the transgene is expressed in cells of the animal at a level sufficient to produce amounts of the fusion protein that are sufficient to inhibit transcription of the tet operator-linked gene of interest, wherein said gene of interest confers a detectable and functional phenotype on the mouse when expressed in the cells of the mouse, wherein the level of transcription of the tet operator-linked gene is increased or decreased in the absence or presence of tetracycline or a tetracycline analogue meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants' attention is drawn to the decision of *The Regents of the University of California v. Eli Lilly and Company* (CAFC, July 1997) wherein it was stated:

In claims involving chemical materials, generic formulas usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate written description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See *Fiers,* 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen*). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly,

naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Because Applicants have failed to provide an adequate written description of the materials used in the compositions and methods claimed and because there is no evidence that Applicants possessed any other animals made with the Applicants' tet system beyond those disclosed and/or known in the prior art, the rejected claims fail to meet the written description requirement under 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11 and 13-28 are rejected under the judicially created doctorine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S.

Patent No. 5, 866, 755 (2/2/99), for reasons of record set forth in the previous office action of 7/8/99, 9/13/01, and 5/21/03.

Applicants' request to hold the double patenting rejection in abeyance until the indication of allowable claims was acknowledged 4/20/04.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 27, 35, 40, 44, 46 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 22, 51-54 of copending Application No. 09/874,389. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

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